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Application of microcrystalline cellulose obtained from *Gossypium herbaceum* in direct compression of chlorpheniramine maleate tablets

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Abstract

The flow, tableting and in vitro release properties of directly compressed chlorpheniramine maleate (CPM) tablets containing fluid bed dried and lyophilized microcrystalline cellulose (MCC) obtained from *Gossypium herbaceum* (GH) were investigated. Delignification of dried GH linters was done through the soda process to obtain alpha cellulose which was hydrolyzed with 2.0 N hydrochloric acid to get MCC. The MCC was washed with water until neutral. Drying was done by either fluid bed method or lyophilization to obtain MCC-*GossF* and MCC-*GossL* respectively. Chlorpheniramine tablets containing 20, 30 and 40% of the MCCs were prepared by direct compression method. Avicel PH102 (AVH-102) served as comparing standard. Using standard methods, evaluation of the powders and the tablets was done. The evaluated parameters of the powders and tablets conformed to the British Pharmacopoeia specifications. The CPM tablets containing MCC-GossF (coded CGF) had better flow but were not mechanically as strong as those containing MCC-GossL (coded CGL). The hardness and disintegration times of the tablets were in the order of CGF < CGL and the friability was in the order of CGF > CGL. Similar parameters of DCL compared well with CPM tablets containing AVH-102 (coded DAV). The MCC obtained from GH had dilution potential up to 40% except in CGF-4 tablets. The *in vitro* dissolution showed > 80% CPM release from all the batches within 30 min. The release kinetics were of mixed order while the mechanism of drug release was Fickian. The MCCs served as good directly compressible binder for chlorpheniramine maleate.

Keywords: *Gossypium herbaceum*; Direct compression; Microcrystalline cellulose; Chlorpheniramine maleate; Tablet

1. Introduction

Direct compression technology is a process that involves the direct compression of the powder or granule blends of the API and suitable excipients into a firm compact. It is regarded as the most advanced form of tablet manufacture through compression in that the powder blend is neither pre-treated by wet or dry granulation methods [1]. The Active Pharmaceutical Ingredient (API) and excipients are pulverized and classified (where necessary) to desired particle sizes, mixed and compressed [2,3]. Consequently, moisture and heat sensitive substances are manufactured without loss of integrity to the chemical and therapeutic characteristic. Some other advantages of this method over the dry granulation and wet granulation methods include: less number of processing steps, fewer unit operations, less machinery, reduced number of personnel, reduced processing time and increased product stability [4,5]. The product would have adequate chemical stability as it ages since heat and moisture were not introduced during its manufacture [3]. Since the formation of larger particle agglomerates from small drug particles through a binding process is not applicable in direct compression, tablets prepared by this method would disintegrate faster than when wet or dry granulation methods are used [3]. This is a result of the fast penetration of water into the hydrophilic tablet matrix by

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capillary action of the pores and subsequent disruption of hydrogen bonds [6]. Direct compression has some disadvantages and they include: Poor flow and bonding of particles to a strong compact, poor and inconsistent tablet weight, content uniformity failure, and dissolution failure. Direct compression technology cannot be used in situations where the active drug would consist a high percentage of the tablet bulk (high dose), has poor flow properties, poor compaction properties, and/or low bulk density. This is because filler–binders have a limited dilution potential. Another major disadvantage of direct compression technology is powder segregation and sampling during blending of powders. Segregation may occur because of the differences in the densities of the API and excipient particles. Segregation however, can be limited if the particle size distribution and density of the API and excipients are carefully considered and matched. Since most of the directly compressible excipients have a triple role of diluent/binder/filler, they are expected to have certain attributes such as inertness, good compactibility, good flowability, stability, and batch to batch reproducibility of the API before they can be qualified to be used.

Cellulose and its derivatives such as microcrystalline cellulose have been reported to be useful in the pharmaceutical sector especially in the formulation of tablets [7-9]. Microcystalline cellulose is regarded as the most efficient dry binder available for direct compression of tablets [10,11]. The type of plant from where the MCC is derived could greatly affect its characteristics. These differences can be as a result of variations in the chemical composition, proportion of cellulose, hemicellulose and lignin that is available within the plant as well as the organization structure of the cellulose [12-14]. *Gossypium herbaceum* is a species of cotton native to the semi – arid regions of sub – Saharan Africa and Arabia [15]. Cotton is considered a very valuable if not the most valuable plant fiber in the world. In the textile industry, it is used in the manufacture of fabrics either alone or in combination with other plant, animal or synthetic fibers. Other products made from cotton fiber include paper, automobile upholstery, twine rope, sewing thread, fishing net, plastics, explosives and photographic film. In the pharmaceutical industry, cellulose and its derivatives are abundantly obtained from cotton linters. It has been reported that cotton linters is the highest source of cellulose [16]. Microcrystalline cellulose, a derivative of cellulose has been widely used in the pharmaceutical sector as a stabilizer in suspensions, creams, lotions, as filler and diluent in pharmaceutical tablets [15-17]. Medicinally, extracts from cotton have been used to manage dysmenorrhea, expulsion of the placenta after child birth, increase of lactation in nursing mothers, nausea, diarrhea, prevention of atherosclerosis, and coronary heart disease [18,19].

Chlorpheniramine maleate is a white odorless crystalline powder with a bitter taste. It is one of the most potent anti-histamines. It is very useful in the alleviation of urticarial rashes and nasal allergy [19]. Chlorpheniramine maleate was chosen as API for this study because of not only its therapeutic value but also because of its low therapeutic dose. Amongst other properties, the carrying capacity (dilution potential) of the MCCs obtained from *G. herbaceum* in the chlorpheniramine tablets were established.

2. Methodology

2.1. Materials

Chlorpheniramine maleate (Evans Nig. Plc.), Sodium hydroxide (Merck, Germany), hydrochloric acid (BDH, Poole England), talc, magnesium stearate (Sigma, USA), sodium hypochlorite (JIK, Reckitt & Colman Nig. Plc), Avicel® PH 102 (FMC Biopolymer, USA), *Gossypium herbaceum* bolls.

2.2. Methods

2.2.1. Processing of microcrystalline cellulose.

The method previously reported by Nwachukwu and Ofoefule in the processing of microcrystalline cellulose from *Gossypium herbaceum* was adopted [20]. A quantity of five hundred grams (500 g) of sorted, dried cotton linters was submerged in 95 % v/v ethanol for 12 h to remove any traces of wax from the linters. The alcohol was squeezed off, and the linters were digested in 2.5 % w/v sodium hydroxide at 100 °C for 3 h. It was washed with copious amounts of distilled water until it was neutral to litmus. It was bleached with 0.4 % w/v solution of sodium hypochlorite at 80 ˚C for 30 min and further washed with distilled water until it was neutral to litmus. Further digestion of the fiber was done with 17.5 % w/v NaOH at 100 °C for 1 h. A second bleaching with 0.4 % w/v sodium hypochlorite solution led to the production of a white fluffy alpha (α) cellulose. The α cellulose was dried in an oven (Memmert®, England) at 60 °C for 1 h, and hydrolyzed with 2.0 N hydrochloric acid solution that was heated up to a temperature of 105 °C in a paraffin oil bath for 15 min to obtain microcrystalline cellulose powder. More distilled water was used in washing the MCC until it was neutral to litmus, the water was squeezed off the MCC and the damp MCC was divided into two portions. One portion was dried by fluid bed drying using a Sherwood® Tonado model, China at a temperature of 60 ± 1˚C and inlet air of 30 m3 min-1 for 3 h or lyophilization using a Gallenkamp®, model LGT 18, England at a temperature of – 45 °C for 6 h. The

fluid bed dried MCC was coded MCC-GossF . The other portion was lyophilized and was coded MCC-GossL [9]. Both MCCs were milled and screened through a 250 µm stainless steel sieve (Retsch ®, Germany). The physicochemical, flow and compaction properties of these MCCs have earlier been reported [20].

2.2.2. Formulation of chlorpheniramine maleate tablets

Chlorpheniramine maleate tablets were formulated using MCC-GossF, MCC-GossL and a commercial MCC, AVH-102. The correct quantities of each of the ingredients shown in Table 1 were weighed into a porcelain mortar where they were homogeneously blended using the doubling up technique. Quantities of the powder blends that would enable the production of 100 tablets per batch at a target tablet weight of 300 mg per tablet were prepared.

Table 1 Formula for chlorpheniramine maleate tablets.

Type of MCC	Ingredient / Batch	Diazepam (mg)	Polymer (mg)	Corn starch (mg)	Magnesium stearate (mg)	Talc (mg)	Total (mg)
MCC-GossF	CGF-1	0.00	280.50	15.00	3.00	1.50	300.00
	CGF-2	60.00	220.50	15.00	3.00	1.50	300.00
	CGF-3	90.00	190.50	15.00	3.00	1.50	300.00
	CGF-4	120.00	160.50	15.00	3.00	1.50	300.00
MCC-GossL	CGL-1	0.00	280.50	15.00	3.00	1.50	300.00
	CGL-2	60.00	220.50	15.00	3.00	1.50	300.00
	CGL-3	90.00	190.50	15.00	3.00	1.50	300.00
	CGL-4	120.00	160.50	15.00	3.00	1.50	300.00
AVH-102	CAV-1	0.00	280.50	15.00	3.00	1.50	300.00
	CAV-2	60.00	220.50	15.00	3.00	1.50	300.00
	CAV-3	90.00	190.50	15.00	3.00	1.50	300.00
	CAV-4	120.00	160.50	15.00	3.00	1.50	300.00

2.3. Evaluation of chlorpheniramine maleate formulations

2.3.1. Micromeritic properties

Some micromeritic properties of the different batches of the chlorpheniramine maleate powder formulations shown in Table 1 were evaluated to establish the densities and flow behavior.

Bulk and tapped densities

The bulk density of each of the chlorpheniramine maleate powder blends was determined by pouring 15 g of the powder into a clean dry transparent graduated 50 mL measuring cylinder kept on a flat platform. The volume occupied by the powder in the measuring cylinder was noted as its bulk volume. The determinations were done in three replicates for each batch of the powder blends and the bulk density derived using Equation 1 [21]:

$$\text{Bulk density} = \frac{mass\ of\ powder}{bulk\ volume\ of\ powder} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ 1$$

The chlorpheniramine maleate powder in the measuring cylinder was tapped several times on a padded flat surface until a constant volume of the powder was obtained and was denoted as the tapped volume. The tapped density was determined as the ratio of the mass of the powder against the tapped volume as expressed in Equation 2 [21]:

$$\text{Tapped density} = \frac{mass\ of\ powder}{tapped\ \ volume\ of\ powder} \quad \ldots\ldots\ldots\ldots\ldots\ 2$$

Angle of repose

The angle of repose (AOR) of each powder blend was determined using the Jones and Pilpel method [22] with slight modifications. A 50 g quantity of the chlorpheniramine maleate powder blend with the MCC was poured into an open ended pipe of 3 cm diameter (d) and 60 cm length kept on a sheet of paper spread upon a flat platform. The cylindrical pipe was gradually pulled up causing the powder to form a cone on the flat surface. Both the height (h) of the powder heap formed and its diameter were measured. Three replicate determinations were made and the angle of repose was calculated using Equation 3 [21].

$$AOR = \tan^{-1} \frac{2h}{d} \quad \ldots\ldots 3$$

Hausner's quotient and Carr's Index

The Hausner's quotient and Carr's index for the different chlorpheniramine maleate powder blends were determined from Equations 4 and 5 respectively [23, 24].

$$\text{Hausner's quotient (H.Q.)} = \frac{Dt}{Db} \quad \ldots\ldots 4$$

$$\text{Carr's Index (C.I.)} = \left(1 - \frac{Db}{Dt}\right) \times 100 \quad \ldots\ldots 5$$

Where D_b is the bulk density, and D_t is the tapped density.

2.4. Compression of chlorpheniramine maleate tablets

The different chlorpheniramine maleate powder blends (Table 1) were compressed into tablets using a single punch hydraulic tablet press (Model C, Carver Inc., Winscosin, USA) fitted with a set of flat faced 10 mm stainless steel punches. One hundred (100) tablets were compressed from each chlorpheniramine maleate powder blend at a target weight of 300 mg and at a uniform compression pressure of 9.81 megaPascal (mPa) and dwell time of 30 sec. A batch that did not contain chlorpheniramine maleate (batch I) was also compressed into tablets and used as control.

2.4.1. Evaluation of chlorpheniramine maleate tablets

The chlorpheniramine maleate tablets were kept in a desiccator containing silica gel for a period of 24 h to allow the tablets recover from compression effects. The tablets were evaluated for uniformity of weight, hardness, friability, disintegration, content of active ingredient and dissolution test using standard methods.

Tablet physical appearance

The tablets from each batch of chlorpheniramine maleate tablets were examined physically for odor, color, stains or any physical defects.

Uniformity of weight

Twenty tablets that were randomly selected from each batch of the chlorpheniramine maleate tablets were collectively weighed [25]. The mean weight and coefficient of variation of the tablets were determined. The acceptance or rejection criterion was based on the stipulation by the British Pharmacopoeia 2012 [25].

Hardness test

The hardness of ten tablets randomly selected from each batch of the chlorpheniramine maleate tablet formulations were determined using a hardness tester, TBH 100 (Erweka, Germany) and the value at which each tablet broke was recorded. The mean value and standard deviation were determined per batch [25].

Friability test

Ten tablets that were randomly selected from each batch of the chlorpheniramine maleate tablets were dusted of any adhering powder particles, collectively weighed and put in one of the drums of the friabilator, model TAR 200 (Erweka®, Germany) twin drum electronic friabilator programmed to revolve at 25 rotations per minute (rpm) for 4 min. The tablets were removed from the friabilator, de-dusted and any broken tablets rejected. The tablets were reweighed collectively and the friability (F) calculated from Equation 6 [5, 26, 27].

$$F = \left(\frac{Wo-W}{Wo}\right) \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 6$$

Where W_o is the initial weight and W is the final weight.

Disintegration test

Six tablets were randomly selected from each batch of the chlorpheniramine maleate tablets. A model ZT-3 disintegration tester (Erweka®, Germany) was used. One tablet was put in each of the six tubes of the basket of the disintegration test apparatus and held in place with a glass disc. The basket was dipped inside a 1 L beaker containing 500 mL of 0.1N HCl solution warmed up to 37 ± 1˚C and an oscillation speed set at 29 ± 1 cycle per minute (cpm). The time taken for the last tablet to break up completely and pass through the mesh was noted [25]. The mean and standard deviations of the disintegration times were calculated.

Determination of wavelength of maximum absorption (λ_{max}) of chlorpheniramine maleate

A quantity of 100 mg of the pure chlorpheniramine maleate powder was dissolved in sufficient 0.1 N HCl in a 100 mL volumetric flask and the volume was made up to the 100 mL mark with the 0.1 N HCl [25] to obtain the stock solution. The stock solution was serially diluted to obtain chlorpheniramine maleate concentrations of 0.20 mg %, 0.40 mg %, 0.60 mg % and 0.80 mg % strength. Scanning of the 0.20 mg % solution was done in a Jenway 6405 UV/vis spectrophotometer (Jenway®, England) at wavelengths ranging from 220 to 400 nm to obtain the maximum/peak absorbance (**λ_{max}**) of chlorpheniramine maleate at 265 nm**.**

Standard calibration curve of chlorpheniramine maleate

The serially diluted solutions of chlorpheniramine maleate containing 0.20 mg %, 0.40 mg %, 0.60 mg %, 0.80 mg % and 1.00 mg % were placed in a quartz cuvette and their absorbance's read in a UV/Vis spectrophotometer (Jenway®, England) set at a wavelength of 265 nm. A plot of the concentrations against absorbance readings was made and the slope determined.

Assay of chlorpheniramine maleate tablet

Twenty tablets were selected at random from each batch of the chlorpheniramine maleate tablets and were weighed collectively, pulverized in a porcelain mortar and an amount of powder equivalent to the weight of one tablet was taken and dispersed in 5 mL of distilled water in a 100 mL volumetric flask. The filtrate obtained from the dispersion was diluted and the absorbance was read at 265 nm of the Jenway 6405 UV/Vis spectrophotometer [25]. The absorbance's obtained for the tablets from the different batches were correlated with the standard calibration curve earlier established and their concentrations determined using the standard calibration Equation which is stated as [25]:

$$Y = MX + C \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 7$$

Where Y is absorbance, X is concentration and M is the slope.

Dissolution studies of chlorpheniramine maleate

The dissolution or drug release studies of the chlorpheniramine maleate tablets were conducted using a six station model DT 600 (Erweka, Germany) dissolution equipment. The paddle method was used for the evaluation. Each beaker containing 900 mL of 0.1 N HCl solution was heated up to a temperature of 37.0 ± 0.5˚C, and the paddle was set at a speed of 100 rotations per min (rpm) [16]. One tablet was placed in each beaker for the test. Five (5 mL) samples were withdrawn at 10 min intervals up to 30 min with an equal replacement with dissolution medium maintained at 37.0 ± 0.5˚C after each withdrawal. The absorbance readings of the filtrates obtained from the withdrawn samples were determined using a Jenway 6405 spectrophotometer at a wavelength of 265 nm. The absorbance results were converted to concentrations from the standard calibration curve previously determined for diazepam. This was done for all the batches of the diazepam tablets.

2.5. Kinetics and mechanism of chlorpheniramine maleate release

Zero order, First order, Higuchi square root kinetics and Korsmeyer-Peppas models [28,29] were used to evaluate the dissolution profile data obtained from the different tablet formulations in order to ascertain the kinetics and mechanism of chlorpheniramine maleate release.

2.6. Statistical analysis

The data obtained were statistically analyzed using one way ANOVA (IBM SPSS® version 21, USA). Values were considered significant at $p < 0.05$.

3. Results and discussion

3.1. Micromeritic properties

Some of the micromeritic properties obtained from the evaluation of the different chlorpheniramine maleate blends containing the MCCs are shown in Table 2. The bulk and tapped densities of the control batches of the different MCCs (CGF-1, CGL-1 and CAV-1) were lower than the batches containing chlorpheniramine maleate. It was observed that the bulk and tapped densities of the different batches of chlorpheniramine maleate increased as the quantity of chlorpheniramine maleate content of the powder bed was increased and MCC content decreased. This characteristic affirms that the formulations of the powders were compressible and would produce firm tablets on compression using a tablet press. The angle of repose of the different powders containing fluid bed dried MCC (CGF-2 to CGF-4) and CAV-2 to CAV-4 ranged from 27.16 ± 0.55 to 28.45 ± 0.36° and falls under the category of excellent flowing powders [25,30-33] while CGL-2 to CGL-4 batches showed good flow (Table 2). The flow rates observed was in the order of CAVs > CGFs > CGLs. The Hausner's quotient of CGF-2 to CGF-4 showed good flow, CAV-2 to CAV-4 showed fair flow while CGL-2 to CGL-4 showed passable flow (Table 2) [25, 30-33]. Carr's index shows that the CGF and CAV powders had a good flow, while the CGL powders had a passable flow [25, 30-33]. Correlating the different flow parameters, the CGF powders had better flow than both CAV and CGL powder formulations.

Table 2 Some micromeritic properties of chlorpheniramine maleate powder blends.

Batch	Bulk density (g/mL)	Tapped density (g/mL)	Angle of repose (°)	Flow rate (g/sec)	Hausner's Quotient	Carr's Index (%)
CGF-1	0.32± 1.20	0.39 ± 0.75	29.81 ± 1.00	4.25 ± 0.05	1.22 ± 0.90	17.34 ± 0.26
CGF-2	0.37± 0.98	0.44 ± 0.80	28.45 ± 0.36	4.98 ± 0.02	1.18 ± 0.85	15.31 ± 0.60
CGF-3	0.40 ± 0.95	0.47 ± 0.32	27.32 ± 1.10	5.45 ± 0.01	1.18 ± 0.41	14.89 ± 0.39
CGF-4	0.44± 0.80	0.51 ± 0.25	27.16 ± 0.55	5.88 ± 0.01	1.15 ± 0.32	13.73 ± 0.31
CGL-1	0.27 ± 0.87	0.38 ± 0.66	34.10 ± 0.88	No Flow	1.41 ± 0.69	28.34 ± 0.57
CGL-2	0.30 ± 1.00	0.40 ± 0.84	33.25 ± 0.42	1.34 ± 0.14	1.33 ± 0.85	25.00 ± 0.72
CGL-3	0.32 ± 0.96	0.41 ± 0.57	31.76 ± 0.24	1.79 ± 0.25	1.28 ± 0.67	21.35 ± 0.54
CGL-4	0.36 ± 0.76	0.47 ± 0.55	30.35 ± 1.15	1.93 ± 0.03	1.31 ± 0.60	23.40 ± 0.38
CAV-1	0.31 ± 0.64	0.38 ± 0.12	29.55 ± 0.12	3.67 ± 0.90	1.23 ± 0.15	18.40 ± 0.15
CAV-2	0.30 ± 0.45	0.36 ± 0.43	28.22 ± 0.81	5.02 ± 0.10	1.20 ± 0.42	16.67 ± 0.28
CAV-3	0.32 ± 0.51	0.39 ± 0.16	28.15 ± 0.32	5.61 ± 0.15	1.22 ± 0.33	17.34 ± 0.25
CAV-4	0.33 ± 0.64	0.41 ± 0.20	27.87 ± 0.45	5.83 ± 0.02	1.24 ± 0.42	19.51 ± 0.20

3.2. Chlorpheniramine maleate tablets characteristics

3.2.1. Physical inspection

The tablets were circular, flat faced and milk colored. Physical inspection of the tablets showed that there were no defects like chipping, capping or breakages. They were devoid of deformities and can be regarded as good tablets.

3.2.2. Uniformity of weight

Table 3 contains the weight of the chlorpheniramine maleate tablets. The tablet weights were in the range of 295.75 ± 1.84 to 308.15 mg ± 2.17 %. The tablets passed the uniformity of weight test since they were within the British Pharmacopoeia specifications for uncoated tablets [25].

3.2.3. Hardness

The hardness of the tablets are shown in Table 3. All the tablets had hardness values above 40 N and therefore can be assessed to have passed the hardness test. Tablets with hardness of not less than 39.23 N are classified by the BP as good. Such tablets should be strong enough to withstand the undesirable stresses of handling and transportation that the tablet may undergo [25]. The higher the concentration of the API, the weaker the tablets became and also the higher the amount of MCC that is contained in the tablet, the stronger the tablets were observed to be. This is seen in the control batches that had no chlorpheniramine maleate in them, which had significantly higher hardness ($p < 0.05$) than those containing chlorpheniramine maleate. At 20 and 30 % w/w concentrations of chlorpheniramine maleate, the hardness of the tablets formulated with the different MCCs were in the order CGL > CAV > CGF.

3.2.4. Disintegration

The results of the disintegration time of the chlorpheniramine maleate tablets are shown in Table 3. The disintegration times ranged from 0.35 ± 0.05 to 4.33 ± 0.04 min for CGF-1 to CGF-4 tablets, 3.34 ± 0.17 to 4.17 ± 0.96 min for CGL-1 to CGL-4 tablets and 0.26 ± 0.05 to 10.22 ± 0.86 min for CAV-1 to CAV-4 tablets. All the batches of tablets containing the different MCCs disintegrated within 15 min and therefore passed the disintegration time test for uncoated tablets implying that they would release their API for dissolution and absorption within 15 min [25].

3.2.5. Friability

Table 3 contains the friability results of the chlorpheniramine maleate tablets. Generally, there was an increase in the friability of the tablets as the quantity of the chlorpheniramine maleate contained increased. Since friability is a measure of the effects of abrasion on the tablets, an increase in the quantity of the chlorpheniramine maleate content of the tablet causes a weaker and more abrasive tablet. The tablets containing 40% of the API were more friable than others. The order of friability was 40 % > 30 % > 20 % > 0 %. At similar drug concentration, the friabilities varied depending on the type of MCC used. The order of friability was CGF > CAV > CGL. These can be related to the hardness of the tablets (Table 3). Thus, CGL tablets which were the most mechanically strong tablets based on the friability results. With the exception of CGF-4 and CAV-4 batches, all other batches are considered adequate in terms of friability.

3.2.6. Dilution potential

The dilution potential was assessed on the capacity of the tablet to maintain good physical attributes after their excipient content have been diluted with the API. This implies that the tablets must possess good hardness and friability indices that would enable the maintenance of the physical integrity of the tablet. The tablets hardness-friability ratio (H-FR) was used for the assessment and tablets whose values were less than 39.23. Such tablets were considered weak in terms of physical fitness. This is because hardness of ≥ 39.23 N and friability of ≤ 1 % are the set limits for physically strong tablets by both parameters [25]. The results in Table 3 show that all the batches were diluted up to 40 % with chlorpheniramine maleate except for CGF-4. Thus for the CGF batches of tablets, dilutions were made up to 30 % with chlorpheniramine maleate for tablets with good physical integrity to be obtained. The other batches of tablets were diluted up to 40 %. For all the tablet batches, except batch CGF-4, the carrying capacity or dilution potential of the MCCs is 40 %.

3.2.7. Assay of chlorpheniramine maleate tablets

Assay results at the time of formulation show the content of chlorpheniramine maleate to be in the range of 99.37 ± 0.64 to 100.24 ± 1.08 % (Table 3). These values fall within the BP acceptable range for chlorpheniramine maleate tablets which is given as not less than 90 % or more than 110 % of the labeled amount [25].

Table 3 Some physical parameters of chlorpheniramine maleate tablets.

Batch	Weight uniformity [mg*± CV (%)]	Hardness (N)	Friability (%)	Disintegration time (min)	Hardness – Friability Ratio (H-FR)	Assay/Drug content (%)
CGF-1	297.50 ± 0.21	143.37 ± 1.34	0.67 ± 0.05	1.19 ± 0.02	213.38	0.00 ± 0.00
CGF-2	295.75 ± 1.84	55.41 ± 0.20	0.73 ± 0.08	1.36 ± 0.14	75.91	99.37 ± 0.64
CGF-3	299.25 ±1.64	49.54 ± 0.18	0.94 ± 0.04	4.33 ±0.04	52.70	100.08 ± 0.16
CGF-4	300.25 ± 1.69	40.03 ± 0.10	2.33 ± 0.33	0.35 ± 0.05	17.18	100.07 ± 0.16
CGL-1	299.60 ± 7.22	194.07 ± 1.52	0.47 ± 0.02	3.34 ± 0.17	373.21	0.00 ± 0.00
CGL-2	298.90 ± 3.22	64.34 ± 0.09	0.47 ± 0.02	4.17 ± 0.96	94.34	99.36 ± 0.82
CGL-3	308.15 ± 2.17	78.87 ± 0.13	0.78 ± 0.09	5.41 ± 0.11	83.35	99.94 ± 0.11
CGL-4	302.20 ± 2.47	64.55 ± 0.19	0.92 ± 0.07	5.69 ± 0.27	70.16	99.51 ± 0.22
CAV-1	301.60 ± 2.48	246.54 ± 2.36	0.56 ± 0.05	10.22±0.86	440.25	0.00 ± 0.00
CAV-2	303.20 ± 1.49	69.36 ± 0.13	0.85 ± 0.09	3.56 ± 0.92	82.18	100.24 ± 1.08
CAV-3	298.65 ± 2.47	63.27 ± 0.15	0.87 ± 0.09	1.26 ± 0.05	73.24	99.75 ± 0.65
CAV-4	297.50 ± 2.30	55.13 ± 0.19	1.02 ± 0.22	0.26 ± 0.05	54.05	100.11 ± 0.13

3.3. Dissolution/release of chlorpheniramine maleate

Figure 1 shows the dissolution profiles of chlorpheniramine maleate from formulations CGF-2, CGF-3, CGF-4, CGL-2, CGL-3, CGL-4, CAV-2, CAV-3 and CAV-4 tablets. There was a sharp release of the chlorpheniramine maleate within 2 min of dissolution in all the formulations and this was followed by gradual incremental release over 30 min. The initial sharp release suggests a burst release of chlorpheniramine maleate from the tablets. Drug release from the tablets containing the fluid bed dried GH-MCC (CGF-2, CGF-3 and CGF-4) was generally higher than that from the tablets containing the lyophilized GH-MCC (CGL-2, CGL-3 and CGL-4) and avicel PH 102 (CAV-2, CAV-3 and CAV-4). This pattern of release can be correlated to the hardness as well as the disintegration times of the tablets containing the different MCCs. Tablets having strong mechanical bonds amongst its particles would be hard and take longer times to disintegrate and this would obviously delay drug release [31].

A comparative evaluation of chlorpheniramine maleate release from the tablets containing the three MCCs at 20 % w/w chlorpheniramine maleate concentration (Fig.1), shows that CGF-2 and CGL-2 tablets were comparably released ($p > 0.05$), while in CAV-2 there was a significantly ($p < 0.05$) decreased release of the drug. In the three batches of tablets (CGF-2, CGL-2, and CAV-2), the chlorpheniramine maleate was released up to 80 % within 30 min and therefore passed the dissolution test as the BP and USP specify that not less than 80 % of the chlorpheniramine maleate content of the tablet should be released within 30 min [25,30].

At 30 % w/w chlorpheniramine maleate concentration in the tablets, the release pattern of the API showed CGF-3 > CGL-3 and CAV-3 (Fig.1). At the range of 2 – 10 min, CGF-3 had its chlorpheniramine maleate more significantly released ($p < 0.05$) than CGL-3 and CAV-3. Within 4 min, 82.32 % of the drug was released from CGF-3 tablets whereas it took up to 15 min and 25 min for 80 % of the drug to be released from CGL-3 and CAV-3 tablets respectively (Fig.1). The general drug release pattern for all the batches of the tablets showed a gradual incremental pattern. All the batches of tablets met with the BP and USP set criteria for dissolution of chlorpheniramine maleate as there was more than 80 % release/dissolution within 30 min.

At 40 % w/w chlorpheniramine maleate concentration in the tablets, batch CGF-4 had the highest chlorpheniramine maleate release, followed by CGL-4 and CAV-4 batches. There was a significant difference in drug release ($p < 0.05$) between CGF-4 and both CGL-4 and CAV-4 within 10 min while there was no significant difference in amounts of chlorpheniramine maleate released ($p > 0.05$) after 10 min of dissolution. More than 80 % of chlorpheniramine maleate was released in 30 min indicating compliance to the BP and USP specifications.

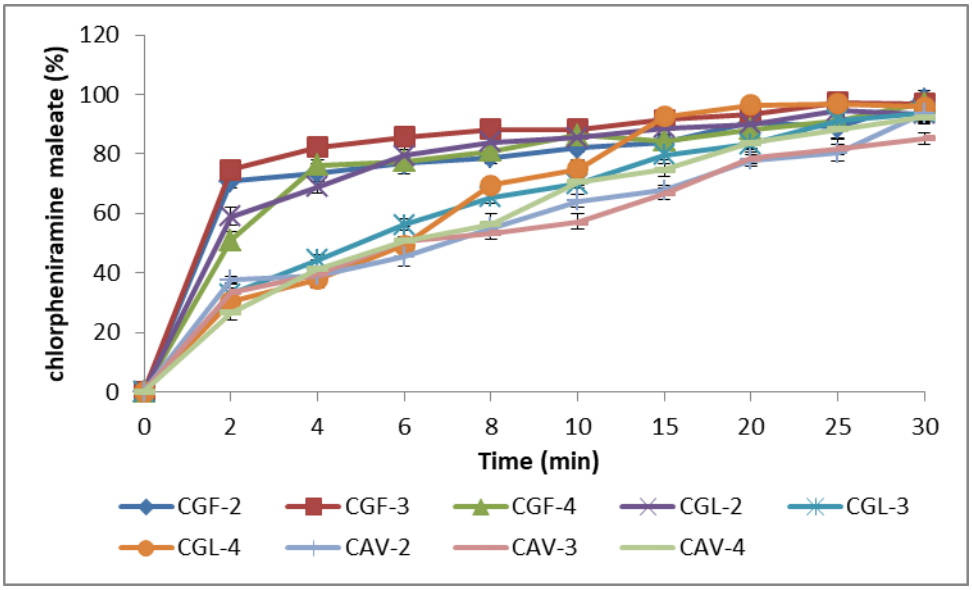

Figure 1 Dissolution profile of chlorpheniramine maleate tablets

3.3.1. Kinetics and mechanism of chlorpheniramine maleate release

The kinetics of chlorpheniramine maleate release from the tablets showed a mixed order kinetics involving Zero order, First order and Higuchi kinetic models. Most of the dissolution from the formulations followed First order kinetics except batch CGL-4 (Zero order), and batches CGF-2 and CAV-2 (Higuchi square root kinetic). The mechanism of drug release for all the formulations was entirely Fickian (Table 4). The correlation coefficience 'R^2' was used to determine the kinetics while 'n' was used to determine the mechanism. Mechanism of release is considered as Fickian when 'n' values are ≤ 0.5 [28].

Table 4 Kinetics and mechanism of chlorpheniramine maleate release from tablet formulations.

Batch/Model	**Zero order kinetic**	**First order kinetic**	**Higuchi square root kinetic**	**Korsmeyer-Peppas**	
	R^2	R^2	R^2	R^2	n
CGF-2	0.5633	0.7927	0.9564	0.9312	0.1109
CGF-3	0.4908	0.9367	0.9212	0.9593	0.0948
CGF-4	0.6351	0.8637	0.7568	0.8201	0.1893
CGL-2	0.6267	0.895	0.8356	0.9074	0.1604
CGL-3	0.9081	0.9896	0.9565	0.9731	0.3826
CGL-4	0.9128	0.8856	0.8903	0.9308	0.4772
CAV-2	0.9202	0.9156	0.9710	0.9546	0.3569
CAV-3	0.9115	0.9890	0.9860	0.9862	0.3598
CAV-4	0.9377	0.9886	0.9557	0.9680	0.4556

4. Conclusion

The bulk and tapped densities of the powder show that both indices increased with increase in the content of the API which implies that there was a reduction in the volume of the powder as the agitation or tapping of the powder bed

increased. The flow parameters generally show the powders to have a good flow. The CGF powder blends had better flow properties than the DGL powders. The powder formulations resulted in good tablets on compression except for CGF-4 batch of tablets that showed physical weakness. The tablets containing the lyophilized powder (MCC-GossL) and AVH-102 were stronger than those containing the fluid bed dried powder (MCC-GossF). All the batches of tablets passed the uniformity of weight, crushing strength and friability tests except batch CGF-4 that failed the crushing strength and friability tests. All the tablets also passed the disintegration time, assay, dissolution/drug release and stability tests based on the British Pharmacopoeia set limits. The MCCs were diluted up to 40 % w/w with chlorpheniramine maleate except MCC-GossF which was diluted up to 30 % w/w. A mixed order of kinetics was observed while a uniform mechanism (Fickian) was predominant in the drug release from the tablets. Microcrystalline cellulose obtained from *Gossypium herbaceum* served as good carrier for chlorpheniramine maleate tablets.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there are no conflict of interest

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